American Journal of Hematology 56:193–196 (1997)

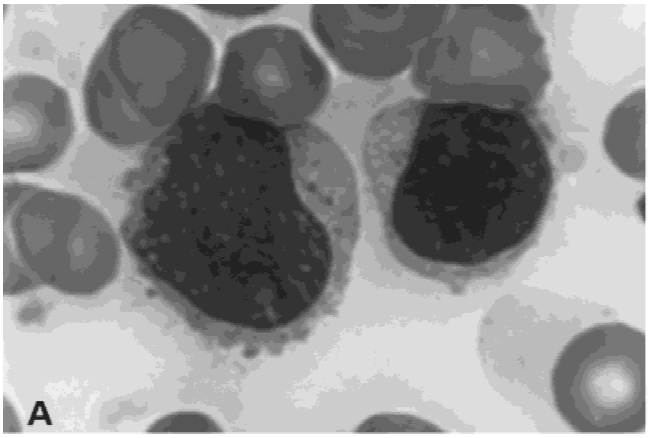
LETTERS AND CORRESPONDENCE

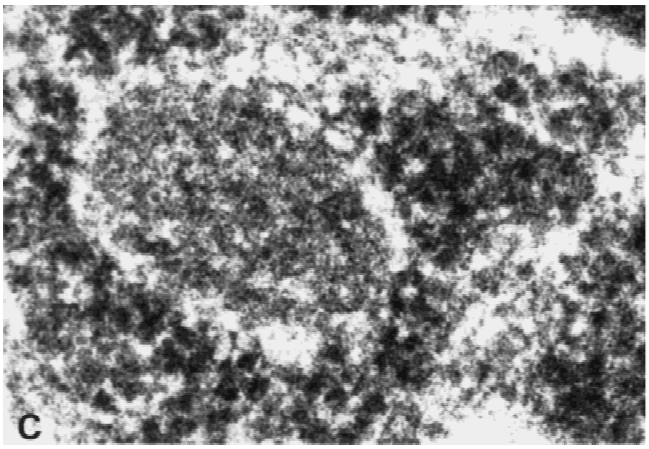
Letters and correspondence submitted for possible publication must be identified as such. Text length must not exceed 500 words and five bibliographic references. A single concise figure or table may be included if it is essential to support the communication. Letters not typed double-spaced will not be considered for publication. Letters not meeting these specifications will not be returned to authors. Letters to the Editor *are utilized to communicate a single novel observation or finding.* Correspondence *is to be used to supplement or constructively comment on the contents of a publication in the journal and cannot exceed the restrictions for* Letters to the Editor. *The Editor reserves the right to shorten text, delete objectional comments, and make other changes to comply with the style of the journal. Permission for publication must be appended as a postscript. Submissions must be sent to Marcel E. Conrad, M.D., Associate Editor,* American Journal of Hematology, *USA Cancer Center, Mobile, Alabama 36688 to permit rapid consideration for publication.*

T-Acute Lymphoblastic Leukemia With Cytoplasmic Granules

To the Editor: Granular acute lymphoblastic leukemia (ALL) is a morphological variant of ALL, and is characterized by the presence of prominent azurophilic granules or inclusions in the cytoplasm of the lymphoblasts. The prevalence of granular ALL ranges from 1.7 to 7% of all ALLs, depending on its definition in terms of percentage of blasts possessing granules [1–4]. Most series showed the predilection of common-ALL phenotype [1–3]. The presence of cytoplasmic granules in T-lineage leukemic blasts was rarely described [4,5]. We report here a case of childhood granular T-ALL.

A 7-year-old Chinese boy was admitted into the Department of Pediatrics at Prince of Wales Hospital in Hong Kong with a history of fever and pallor for a month, and subsequent symptoms of bleeding tendency. There was no family history of malignancy or blood disorder. Physical exami-





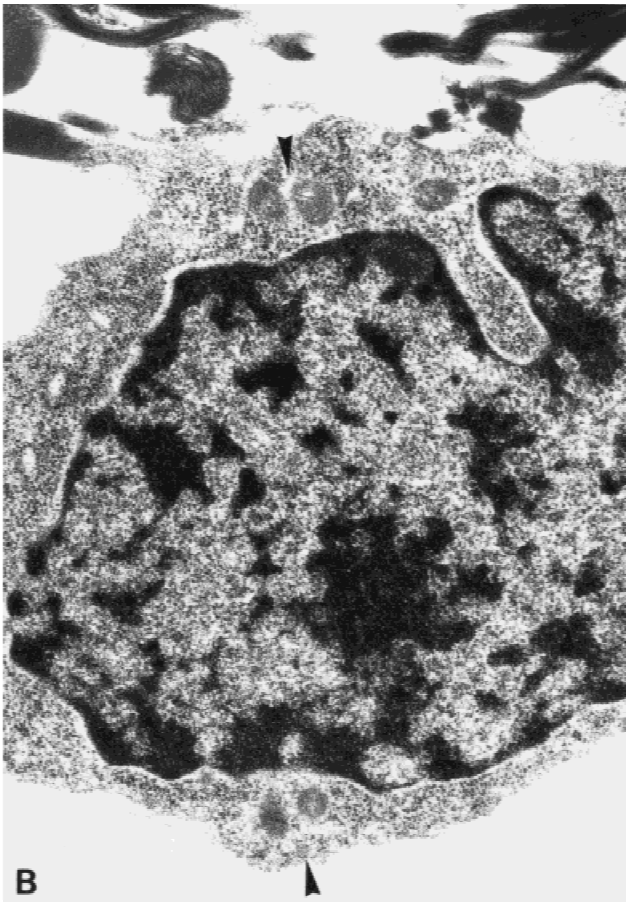


Fig. 1. A: Lymphoblasts containing azurophilic cytoplasm granules; peripheral blood, ×1,000. B: Appearance of cytoplasmic granules as non-membrane-bound amorphous materials; EM, ×10,000 (arrowheads). C: Higher power of one of the granules; EM, ×105,000.

nation revealed hepatomegaly measuring 3 cm below the right coastal margin and splenomegaly measuring 7 cm below the left. There was generalized lymphadenopathy, but the testes and central nervous system were normal. Complete blood count during admission showed hemoglobin 9.8 g/dL, platelet 80.0 × 10^9/L, WBC 140.0 × 10^9/L; differential: blasts 86%, neutrophils 1%, lymphocytes 13%, and occasional nucleated red blood cells. Bone marrow examination showed several hypercellular flakes that were filled totally with heterogeneous lymphoblasts. The blasts were 2 to 3 times the diameter of adjacent red cells, had a moderate amount of basophilic cytoplasm, and oval to irregular nuclei with 1 or 2 conspicuous nucleoli. This ALL was classified as L2 according to the FAB recommendation. Two to five small, but prominent, azurophilic granules were noted in 23% of the blasts (Fig. 1). No Auer rods were seen. Cytochemical studies showed that the blasts were inert to Sudan Black B and nonspecific esterase, but the granules were positive for acid phosphatase and PAS. Flow cytometric analysis revealed positivities to T-markers (CD2, CD3, and CD7), and were negative for HLA-DR, B-lineage markers (CD10, CD19, and CD20) and myeloid markers (CD13 and CD33). Electron microscopy (EM) showed that the cytoplasmic granules appeared as oval non-membrane-bound amorphous materials (Fig. 1). Cytogenetic study revealed no chromosomal aberrations. CT scan of the thorax was negative for any mediastinal mass.

The patient was treated with induction chemotherapy including vincristine, l-asparaginase, and prednisolone. Remission was achieved and 3 blocks of intensification were subsequently given. Central nervous system prophylaxis with 1,800 cGy of cranial irradiation and a total of 8 doses of intrathecal methotrexate were also given. The patient tolerated the chemotherapy well.

Results of EM studies (mostly common-ALL) on the cytoplasmic granulations were non-concordant in that they have been reported to appear as lysozyme in dysplastic organelles [1], membrane-bound vesicles containing amorphous materials [2], parallel tubular arrays, collections of virus-like vesicles, detached masses of nuclear chromatin, and other unidentified structures [5]. Our EM findings of non-membrane-bound amorphous material of unidentifiable origin were in concordance with those of Smith and Collins, the only report in the literature that described EM findings in granular T-ALL [5].

Darbyshire and Lilleyman found that there were no correlations between granular ALL of childhood and specific karyotypes [1]. Cytogenetic study was normal in our case too. Prognostic values of granular ALL were controversial. Some studies demonstrated no prognostic significance [1,3] while others concluded that granular ALL fared worse on account of its L2 morphology [2,4]. In our case, complete remission was achieved and there was no evidence of relapse after 12 months of follow-up.

Wai-Chiu Tsoi
Howard D.H. Lai
Chi-Shun Feng
Departments of Anatomical and Cellular Pathology and Paediatrics, Prince of Wales Hospital, Shatin, NT, Hong Kong

REFERENCES

1. Darbyshire PJ, Lilleyman JS: Granular acute lymphoblastic leukaemia of childhood: A morphological phenomenon. J Clin Pathol 40:251–253, 1987.
2. Cantu-Rajnoldi A, Invernizzi R, Biondi A, Banfi P, Zoia A, De Fazio P, Polli N: Biological and clinical features of acute lymphoblastic leukaemia with cytoplasmic granules or inclusions: Description of eight cases. Br J Haematol 73:309–314, 1989.
3. Invernizzi R, Rosanda C, Basso G, Conter V, Di Cataldo A, Fenu S, Forni M, Frappampina V, Granchi D, Locatelli F, Miano C, Santostasi T, Cantu-Rajnoldi A: Granular acute lymphoblastic leukemia in children. Haematologica 77:30–34, 1992.
4. Cerezo L, Shuster JJ, Pullen J, Brock B, Borowitz MJ, Falletta JM, Crist WM, Head DR: Laboratory correlates and prognostic significance of granular acute lymphoblastic leukemia in children: a pediatric oncology group study. Am J Clin Pathol 95:526–531, 1991.
5. Smith H, Collins RJ: Acute lymphoblastic leukaemia with cytoplasmic granules or inclusions. Br J Haematol 75:440–446, 1990.

Mast Cell Disease Mimicking Granulocytic Sarcoma

To the Editor: Systemic mast cell disease (SMCD) is an idiopathic disorder characterized by abnormal proliferation of mast cells that infiltrate various organs including bone marrow, spleen, liver, skin, and lymph nodes [1]. In approximately 20 to 30% of the patients, it can be associated with other hematologic disorders such as myelodysplastic syndromes, myeloproliferative disorders, and acute myelogenous leukemia [2]. Because of its rarity and its tendency to mimic other more frequent disorders, systemic mast cell disease can be easily underrecognized or misdiagnosed if the hematologist and/or pathologist do not suspect the diagnosis.

A 45-year-old woman presented with a 3-month history of diarrhea and right hip pain. Her evaluation was significant for normochromic, normocytic anemia (hemaglobin 8.2 g/dL) and a normal WBC and platelet count with an elevated absolute eosinophil count between 600 and 1,500 × 10^6/L. In addition, the patient had mildly elevated LDH at 231 U/L (nl 94–210 U/L) and a mildly elevated alkaline phosphatase at 285 U/L (nl 84–218 U/L), due to elevated liver fraction. The rest of the patient's workup, including liver and kidney function, iron studies, endocrine, rheumatologic, and infectious disease workup, was negative. An upper endoscopy with small bowel biopsy looking for sprue and a colonoscopy were negative. A bone scan showed diffusely prominent uptake throughout the axial skeleton. A metastatic bone survey showed a large lytic destructive lesion involving the left acetabulum, ilium, and ischium with an associated soft tissue mass. CT of the abdomen was negative with the exception of the pelvic lytic lesion. A CT-guided biopsy of the lesion showed diffuse involvement by undifferentiated mononuclear cells with blastic vs. lymphomatoid morphology (Fig. 1A). Occasional eosinophilic myelocytes were also present. Immunoperoxidase stains performed on frozen and paraffin sections showed the neoplastic cells to be positive for CD43 but essentially negative for any other granulocyte, T cell, or B cell marker including myeloperoxidase, CD3, CD5, CD7, CD10, CD20, CD23, and κ and λ immunoglobulin light chains. With both CD43 positivity and the presence of eosinophils in the biopsy sample, the final pathologic diagnosis was granulocytic sarcoma. A bone marrow biopsy was subsequently obtained and showed fibrosis with atypical megakaryocytes and diffuse infiltration by eosinophils. Because of the extent of the hypereosinophilia, mast cell disease was considered. The tryptase (aminocaproate esterase) stain was positive in both the bone marrow and the needle biopsy of the pelvic lesion (Fig. 1B), proving it to be a mastocytoma rather than a granulocytic sarcoma. Factor VIII antigen and reticulin stains confirmed that the patient had an atypical myeloproliferative disease coexisting with her systemic mast cell disease.

Our case illustrates the difficulty of suspecting the diagnosis of systemic mast cell disease, especially when the typical cutaneous manifestation of urticaria pigmentosa is not present. Symptoms and findings in our patient such as diarrhea and eosinophilia have been reported in up to 30 and 25%, respectively, of the patients with systemic mast cell disease [1,3]. Their combination, however, can be part of a broad differential diagnosis from parasitic and neoplastic diseases to inflammatory bowel disease. If mast cell disease is suspected, a 24-hr urine collection for methylimidazoleacetic acid (MIAA) or 11-β-prostaglandin F_{2a} can point toward the diagnosis, if elevated. However, tissue diagnosis, usually by means of a bone marrow biopsy, is necessary for confirmation [1]. Use of immunostaining requires careful interpretation, since mast cells can be CD43 positive mimicking granulocytic sarcoma (as in our patient) or T-cell lymphoma, CD68 positive mimicking histiocytic disease, or tartrate resistant acid phosphatase

(TRAP) positive mimicking hairy cell leukemia. In our experience, the tryptase stain is the most reliable stain for identification of mast cells in tissue or bone marrow biopsy samples [4].

E. Galanis
C-Y. Li
R. Phyliky

Departments of Internal Medicine, Hematology, and Laboratory Medicine and Pathology, Mayo Clinic and Foundation, Rochester, Minnesota

References

1. Travis WD, Li CY, Bergstralh EJ, Yam LT, Swee RG: Systemic mast disease. Analysis of 58 cases and literature review. Medicine 67:345, 1988.
2. Travis WD, Li CH, Yam LT, Bergstralh EJ, Swee RG: Significance of systemic mast cell disease with associated hematologic disorders. Cancer 62:965–972, 1988.
3. Horan RF, Austen KF: Systemic mastocytosis: Retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. J Invest Dermatol 96:5S–14S, 1991.
4. Hughes DM, Kurtin PJ, Hanson CA, Li C-Y: Identification of normal and neoplastic mast cells by immunohistochemical demonstration of tryptase in paraffin sections. J Surg Pathol 1:87–96, 1995.

Simultaneous Occurrence of Lupus Anticoagulant and Factor VIII Inhibitors

To the Editor: I read with interest the Letter to the Editor in the March 1996 issue describing the rare occurrence of a lupus anticoagulant (LA) and a factor VIII inhibitor in a patient with a localized pemphigoid [1]. Based on a prolonged APTT and failure to correct on the addition of normal plasma (1 part patient, 1 part normal), the authors correctly diagnosed an acquired circulating anticoagulant. They performed a Staclot LA® (Diagnostica Stago, Asnieres, France) procedure, which resulted in neutralization of the inhibitor [2]. With these findings, they concluded the patient had an LA. Due to the severity of bleeding in the patient, they also performed factor assays that identified a factor VIII level of 2% and a factor VIII inhibitor titer of 32 Bethesda units.

The authors were apparently unaware of false-positive Staclot LA results seen in the presence of factor VIII inhibitors [2,3]. In the setting of a bleeding diathesis with an acquired inhibitor, it is necessary to perform another confirmatory procedure (e.g., dilute Russell Viper Venom Time/ confirmatory Russell Viper Venom Time) [3,4]. It is critically important to differentiate an LA from a factor VIII inhibitor. Failure to do so may result in catastrophic bleeding. A previous paper in the literature reports on the simultaneous occurrence of an LA and an autoantibody to factor VIII [5]. Once again, in this paper, rigorous criteria to establish the presence of an LA were not employed. Adherence to the appropriate diagnostic criteria as recommended by the SCC Subcommittee on Lupus Anticoagulant/ Phospholipid-Dependent Antibodies is extremely important [4]. Failure to

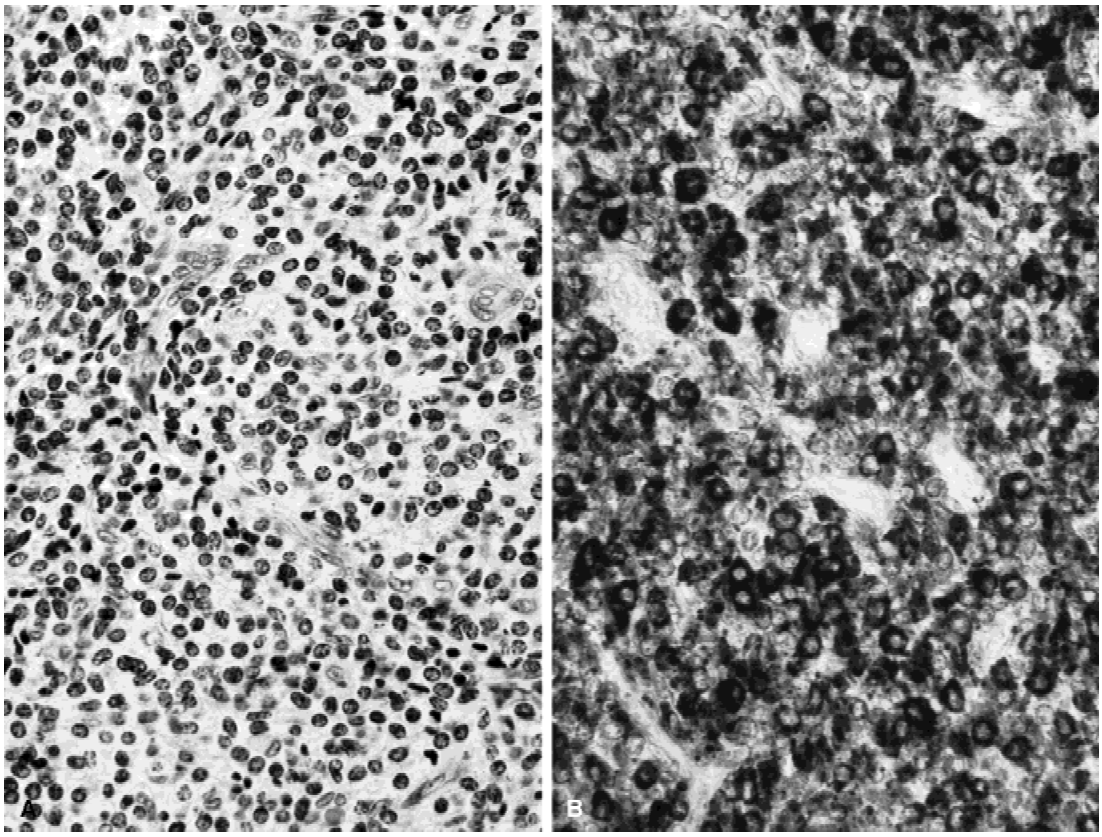


Fig. 1. A: Section of the left iliac wing lesion showing monomorphic mononuclear cells with clear cytoplasm suggestive of hematolymphoid neoplasm (H & B stain, ×256). B: Section of the same lesion showing that the neoplastic cells are strongly positive for tryptase, establishing the diagnosis of mastocytoma (Immunoperoxidase stain for tryptase, ×256). The cells were also positive for CD43 but negative for other lymphoid and granulocytic markers.

do so may result in misdiagnosis and hemorrhage due to a factor VIII inhibitor.

DOUGLAS A. TRIPLETT
Midwest Hemostasis and Thrombosis Laboratories, Muncie, Indiana

REFERENCES

1. Biron C, Durand L, Lemkecher T, Dauverchain J, Meunier L, Meynadier J, Schved JF: Simultaneous occurrence of lupus anticoagulant, factor VIII inhibitor and localized pemphigoid. Am J Hematol 51:250–251, 1996.
2. Triplett DA, Barna LK, Unger GA: A hexagonal (II) phase phospholipid neutralization assay for lupus anticoagulant identification. Thromb Haemost 70:787–793, 1993.
3. Brandt JT, Barna LK, Triplett DA: Laboratory identification of lupus anticoagulants: Results of the second international workshop for identification of lupus anticoagulants. Thromb Haemost 74:1597–1603, 1995.
4. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: An update. Thromb Haemost 74:1185–1190, 1995.
5. Ballard HS, Nyamuswa G. Life-threatening haemorrhage in a patient with rheumatoid arthritis and a lupus anticoagulant coexisting with acquired autoantibodies against factor VIII. Br J Rhemuatol 32:515–517, 1993.